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MAJOR ARTICLE

Performance of an Easy and Simple New Scoring Model in Predicting Multidrug-Resistant Enterobacteriaceae in Community-Acquired Urinary Tract Infections

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Background. Multidrug resistance (MDR) is a growing global problem in bacterial community-acquired urinary tract infections (CUTIs). We aimed to propose an easy-to-use clinical prediction model to identify patients with MDR in CUTI.

Methods. We conducted a retrospective study including 770 patients with documented CUTI diagnosed during 2010–2017. Logistic regression–based prediction scores were calculated based on variables independently associated with MDR. Sensitivities and specificities at various cutoff points were determined, and the area under the receiver operating characteristic curve (AUROC) was computed.

Results. We found MDR Enterobacteriaceae in 372 cases (45.1%). Multivariate analysis showed that age ≥70 years (adjusted odds ratio [aOR], 2.5; 95% confidence interval [CI], 1.8–3.5), diabetes mellitus (aOR, 1.65; 95% CI, 1.19–2.3), history of urinary tract surgery in the last 12 months (aOR, 4.5; 95% CI, 1.22–17), and previous antimicrobial therapy in the last 3 months (aOR, 4.6; 95% CI, 3–7) were independent risk factors of MDR in CUTI. The results of Hosmer-Lemshow chi-square testing were indicative of good calibration of the model (χ^2 = 3.4; P = .49). At a cutoff of ≥2, the score had an AUROC of 0.71, a sensitivity of 70.5%, a specificity of 60%, a positive predictive value of 60%, a negative predictive value of 70%, and an overall diagnostic accuracy of 65%. When the cutoff was raised to 6, the sensitivity dropped (43%), and the specificity increased appreciably (85%).

Conclusions. We developed a novel scoring system that can reliably identify patients likely to be harboring MDR in CUTI.

Keywords. community-acquired urinary tract infection; multidrug resistance; risk factors; score.

Urinary tract infections represent a severe public health problem, with a global burden of about 150 million infected people worldwide [1]. They are one of the most common bacterial community-acquired infections and the most frequent health care–associated infection [1, 2]. Urinary tract infections (UTIs) occur anywhere in the urinary system and are usually due to bacteria from the digestive tract, especially Enterobacteriaceae. Antibiotic resistance is a growing global problem, leading to significant challenges and costs in the health care system. The resistance level of pathogens against commonly used antibiotics in community urinary tract infections (CUTIs) has significantly increased in recent years [3], representing a clinical challenge to physicians in treating CUTI patients. Multidrug-resistant (MDR) organisms cause both health care–associated and community-acquired infections with increasing occurrence [4, 5]. Delays in initiating appropriate and urgent empirical antibiotic therapy contribute to the increased morbidity, severe outcomes such as renal failure, length of stay, and treatment-related costs. Therefore, recognition of risk factors predictive of MDR in UTI is mandatory to identify patients at increased risk of MDR at the time of admission and to administer the adequate treatment to ameliorate the prognosis. Despite the clinical importance of the widespread emergence of these MDR uropathogens, few studies have developed decisional models based on risk stratification tools to accurately predict MDR in the local setting. Given the challenge of determining a priori which patients will ultimately have infection due to an MDR organism, we sought to propose a reliable and easy-to-use clinical prediction model that could be used at hospital admission to identify patients likely to harbor these organisms.

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METHODS

Study Design and Settings

We conducted a retrospective cohort study including patients with documented CUTI diagnosed at the infectious diseases department and its affiliated outpatient consultation department in Hedi

Chaker University Hospital, Tunisia, during the period 2010–2017. This university hospital is the main medical center receiving patients from different governorates of Southern Tunisia. The analysis was conducted according to the STROBE checklist [6].

Inclusion Criteria and Case Definition

We enrolled all inpatients and outpatients with bacteriologically confirmed CUTI who were aged 15 years and older. We included only patients with documented CUTI caused by Enterobacteriaceae isolated from samples collected within 48 hours of symptom onset. Nonfermenters (Acinetobacter, Pseudomonas) were excluded from the analysis. If more than 1 isolate was reported for the same patient, only the initial (index) culture was included in the study. CUTI was defined as the presence of urinary symptoms (dysuria, frequency, urgency, sensing of residual urine) and/or symptoms consistent with active clinical infection: fever (≥38°C) or tenderness of costovertebral angle on physical exam and isolation of uropathogen from urine. CUTI cases with negative urine cultures were excluded from the study. Cystitis was defined by inflammation of the bladder caused by a bacterial infection, characterized by the presence of urinary symptoms. Prostatitis was defined by an inflamed and painful prostate gland due to a bacterial infection isolated in the urine culture. All urine samples were obtained by midstream clean-catch or catheterization from patients who were referred to the microbiological laboratory of the university hospital. All positive urine cultures ($\geq 10^5$ CFU/mL) were referred to the laboratory for confirmation and detection of susceptibility to antibiotics. For identification of isolates, a panel of biochemical tests was used based on standard microbiological methods [7]. Antimicrobial susceptibility testing was carried out by the disc diffusion method with a panel of antimicrobial drugs (Bio-Rad) and was interpreted according to the EUCAST guidelines [8]. The culture method, identification procedures, and reporting system were similar throughout the periods when samples were processed. MDR was defined according to the International Standard Definitions for acquired resistance: nonsusceptible to ≥1 agent in >3 antimicrobial categories [7].

Data Collection

We retrieved data from both laboratory reports and medical records using a standard case record form. Collected data included patient demographics such as gender and age, comorbidities, medical history (prior hospitalization during the 12 months preceding admission, previous CUTI episodes, urinary tract surgery in the previous 12 months, invasive procedures such as permanent urinary catheter, use of antibiotics within the 3 previous months as well as immunosuppressive therapy and chemotherapy during the 3 months preceding the index admission), clinical presentation, site of acquisition, and results of laboratory tests including blood cultures and antimicrobial susceptibility. To reduce the errors of capturing information, 2 investigators exhaustively reviewed the medical records of eligible patients. If any discrepancies were observed, both the authors reviewed the medical records simultaneously, and a decision was reached through consensus.

Statistical Analysis

Statistical analysis was performed using SPSS.20. The results of quantitative variables were presented as mean ± SD or median and interquartile range (IQR), those of qualitative variables as number and percentage. For normally distributed variables, the *t* test was used to compare 2 means, and analysis of variance was used to compare several means. Spearman's correlation coefficient was used to determine chronological trends of MDR prevalence during the study period (*rho*, *P*). For categorical variables, the chi-square test and Fisher exact test were used in independent samples. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association that emerged. Variables associated with MDR isolation in the univariate analysis ($P < .20$) were included in a logistic regression model, and a backward stepwise approach was used to identify independent predictors of MDR (adjusted odds ratio [aOR], 95% CI, *P*). Any variable with a *P* value of ≤.05 was retained in the final model. The final regression model was converted into a point-based rule, with weighted scores assigned to each variable to generate a clinically applicable and decision-making rule for the prediction of MDR. To derive a simple-to-compute risk score, regression coefficients were converted to weighted scores by dividing each regression coefficient by one-half of the smallest coefficient and rounding to the nearest integer [9–11]. For each patient, the individual scores that correspond to the predictors were summed together to produce an overall score ranging from 0 to 14 points. Calibration was assessed using the Hosmer-Lemeshow test for goodness of fit, which evaluated expected and observed probabilities in population deciles. The discriminatory power of the prediction rule was expressed as the area under the receiver operating characteristic curve (AUROC). The sensitivity, specificity, and diagnostic accuracy of the prediction rule were calculated at different cutoff values. Positive and negative predictive values (PPVs, NPVs) were obtained with standard methods. Because we did not have access to an independent data set to validate the clinical decision rule, we used a bootstrapping method for internal validation and to estimate the test characteristics of our rule. This technique develops a series of independent (n = 1000) samples taken from our data with replacement and has been shown to effectively simulate a population distribution when no independent data set is available [12]. *P* value of <.05 was considered statistically significant.

RESULTS

Patients' Demographic and Clinical Characteristics

A total of 770 patients with Enterobacteriaceae isolated from urine met the inclusion criteria during the study period

Table 1. Demographic and Clinical Characteristics of the Study Population

Variables	No.	%
Patients' demographics		
Female	510	66.2
Age ≥70 y	232	30.1
Comorbidities		
Diabetes	237	30.8
Urinary lithiasis	82	10.6
Neurological bladder	40	5.2
Benign prostatic hyperplasia	37	4.8
Chronic kidney disease	31	4
Congenital urological malformation	13	1.7
Urological cancer	11	1.4
Medical history		
Recent hospitalization in the previous 12 mo	96	12.5
Prior B-CUTI due to MDR	48	6.2
History of urinary tract surgery in the previous 12 mo	15	1.9
Indwelling medical devices		
Bladder catheter	35	4.5
Ureteroscopy	5	0.6
Immune suppression	14	1.8
Previous antimicrobial therapy in the last 3 mo	138	17.9
Clinical presentation		
Acute pyelonephritis	683	88.7
Cystitis	64	8.3
Prostatitis	23	3
Positive blood culture	95	12.3

Abbreviations: B-CUTI, bacterial community-acquired urinary tract infection; MDR, multidrug resistance.

(Table 1). Their median age (IQR) was 54 (33–72) years, and 510 cases (66.2%) were females. There were 232 cases (30.1%) aged 70 years and above. Comorbidities included diabetes mellitus in 232 cases (30.1%) and urinary lithiasis in 82 cases (10.6%). For patients' medical history, 96 cases (12.5%) were hospitalized in the previous 12 months, 138 cases (17.9%) used antimicrobial therapy in the last 3 months, and 15 cases (1.9%) had undergone a urinary tract surgery in the previous 12 months. The main clinical presentation of CUTI was acute pyelonephritis in 683 cases (88.7%). Blood cultures were positive in 95 cases (12.3%).

Causative Microorganisms and Multidrug Resistance Prevalence in Urine Samples

The most frequently isolated causative microorganism was *Escherichia coli* in 599 cases (72.7%), followed by *Klebsiella pneumoniae* in 119 cases (14.4%) and *Proteus mirabilis* in 18 cases (2.2%). MDR Enterobacteriaceae were found in 369 cases (47.9%). Susceptibility profiles showed that *E. coli* and *K. pneumoniae* were resistant to third-generation cephalosporins in 33.4% and 55.5%, to fluoroquinolones in 28% and 51.3%, and to aminosides in 20.2% and 43.7%, respectively. As for cotrimoxazole, Enterobacteriaceae were resistant in 41.8% (Table 2).

Trend analysis of MDR prevalence showed a significant increase of the MDR proportion between 2010 and 2017 (*rho* = .77; *P* = .028).

Predictors of Multidrug Resistance in Urinary Tract Infections

Univariate analysis (Supplementary Table 1) showed that factors significantly associated with MDR include age ≥70 years (OR, 2.88; *P* < .001) and diabetes mellitus (OR, 2; *P* < .001). Moreover, urological cancer (OR, 3; *P* = .004), history of urinary tract surgery in the previous 12 months (OR, 4.4; *P* = .012), bladder catheter (OR, 2.8; *P* = .004), and prior CUTI due to MDR (OR, 5.9; *P* < .001) were significantly more frequent in MDR CUTI patients. Recent hospitalization in the previous 12 months and previous antimicrobial therapy in the last 3 months were statistically associated with MDR (OR, 3; *P* < .001; and OR, 3.2; *P* < .001; respectively).

Multivariate analysis using logistic regression (Table 3) showed that age ≥70 years (aOR, 2.6; 95% CI, 1.8–3.7; *P* < .001), diabetes (aOR, 1.63; 95% CI, 1.17–2.3; *P* = .002), history of urinary tract surgery in the last 12 months (aOR, 4; 95% CI, 1.1–14; *P* = .045), and previous antimicrobial therapy in the last 3 months (aOR, 5; 95% CI, 3.2–7.9; *P* < .001) were independent risk factors of MDR in UTI (Table 4). The results of Hosmer-Lemshow chi-square testing (χ^2 = 2.58; *P* = .87) were indicative of good calibration. For internal validation, the independent variables of the cohort model were found to be independently associated with MDR after bootstrapped selection, with similar regression coefficients.

Risk Scoring System Predictive of Multidrug Resistance

A weighted score was assigned to each risk factor found to be independently associated with isolated MDR uropathogens as follows: age ≥70 years: 4 points; diabetes mellitus: 2 points; history of urinary tract surgery: 6 points; and antimicrobial therapy in the last 3 months: 6 points (Table 4). The individual scores were added together to produce an overall weighted score ranging from 0 to 18 points. In our study, the median score value was 2, with extremes of 0 and 16. The AUROC of this score was 0.71 (95% CI, 0.66–0.73; *P* < .001), indicating good predictive power in discriminating MDR. When high risk was defined as an overall score of ≥2, the scoring system had a good sensitivity (70.7%) but lower specificity (60%), a PPV of 61%, an NPV of 70%, and an overall diagnostic accuracy of 66%. When the cutoff was raised to 6, the sensitivity dropped (43%) and the specificity increased appreciably (85%). This cutoff level was associated with a PPV and NPV of 72.5% and 62% and an overall accuracy of 66%. At a higher cutoff point (total weighted score ≥ 12), the specificity and PPV achieved 100% (Table 4).

DISCUSSION

Antimicrobial multidrug resistance is increasing throughout the world. Therefore, it is important to identify factors that stratify patients at high risk for an MDR infection, so that broad-spectrum antibiotics can be reserved for use in these patients. Limiting broad-spectrum empiric antibiotics to patients with

Table 2. Distribution of the Causative Microorganisms Isolated in Urine Culture by Resistance Profile in the Study Population

Microorganism	All Isolates, No. (%)	MDR Isolates, No. (%)	Amoxicillin, No. (%)	Third-Generation Cephalosporins, No. (%)	Fluoroquinolones, No. (%)	Aminosides, No. (%)	Colistin, No. (%)	Carbapenem, No. (%)	Fosfomycin, No. (%)	Cotrimoxazole, No. (%)
Enterobacteria	770 (100)	369 (47.9)	588 (76.3)	285 (37)	247 (32)	186 (24.1)	28 (3.6)	28 (3.6)	30 (3.9)	322 (41.8)
Escherichia coli	599 (72.7)	312 (76.1)	438 (73.1)	200 (33.4)	168 (28)	121 (20.2)	5 (8.3)	7 (1.2)	9 (1.5)	257 (42.9)
Klebsiella pneumoniae	119 (14.4)	64 (17.2)	117 (98.3)	66 (55.5)	61 (51.3)	52 (43.7)	4 (3.3)	17 (14.3)	15 (12.6)	47 (39.5)
Proteus mirabilis	18 (2.2)	8 (2.2)	8 (44.4)	1 (5.6)	6 (33.3)	3 (16.7)	14 (77.7)	0 (0)	1 (5.5)	10 (55.5)
Enterobacter spp.	14 (1.7)	3 (0.8)	13 (92.8)	10 (71.4)	2 (14.3)	2 (14.3)	1 (7.1)	1 (7.1)	2 (14.2)	1 (7.1)
Other enterobacteria	14 (1.7)	4 (1.1)	11 (78.5)	4 (28.6)	5 (35.7)	6 (42.9)	4 (28.5)	1 (7.1)	1 (7.1)	5 (35.7)

Abbreviation: MDR, multidrug-resistant.

proven risk factors can help slow the prevalence of resistance to these antibiotics. Early identification of patients at risk of antibiotic resistance and thus therapy failure is an important part of effective empiric therapy [13]. To address this need, various prediction tools have been created to identify those harboring MDR organisms [14–16].

The problem of MDR is no longer limited to hospital-acquired or health care–associated infections. Multidrug-resistant strains have been reported as important and increasing strains that can spread the resistance among different populations of bacteria [17]. In our study, MDR accounted for 47.9% of all Enterobacteriaceae isolates. This rate remains quite high, compared with previously reported rates, ranging from 19% in Chicago [18] and 25% in Portugal [19] to 36.5% in Germany [13]. A previous review studying the antimicrobial susceptibility of Enterobacteriaceae in Africa showed high resistance rates to β-lactams and fluoroquinolones, notably in Tunisia [20]. *E. coli* and *K. pneumoniae* have acquired plasmids encoding extended-spectrum β-lactamases [1]. These plasmids rapidly spread resistance to third-generation cephalosporins and other antibiotics [1]. In Tunisia, *E. coli* is the main isolated uropathogen in CUTI (58.9%), followed by *K. pneumoniae* (14.5%). Susceptibility profiles have shown high resistance rates of *E. coli* to amoxicillin (62.8%), to cotrimoxazole (40.1%), to fluoroquinolones (16.6%), and to third-generation cephalosporins (9.4%) [21], which were lower than our resistance rate. These alarming findings reflected a substantial increase in the third-generation cephalosporin resistance rate in our population over time. Local national guidelines recommend third-generation cephalosporins for empirical treatment of UTI. Thus, it is important for practitioners to be aware of MDR prevalence outside the hospital and to identify patients with risk factors for resistance.

Common risk factors for MDR infections are not well defined, as most studies have focused on particular subgroups of MDR uropathogens, including extended-spectrum β-lactamase producers (ESBLs) and carbapenem-resistant *K. pneumoniae* (KPC). Previously reported risk factors associated with infections caused by ESBLs include length of hospital stay, presence of central venous or arterial catheters, prior surgery, previous administration of antibiotic, especially second- and third-generation cephalosporins, prior residence in a long-term care facility, presence of a urinary catheter, and chronic hemodialysis [22]. Our findings were in agreement with several previous studies that attempted to evaluate the risk factors of MDR, including diabetes mellitus, recurrent UTI, and advanced age, that were statistically associated with MDR, with ORs from 2 to 3 [23, 24]. It has been reported that prior fluoroquinolone use within 3 months, obstructive uropathy, and health care–associated risks were independently associated with MDR [18]. Furthermore, Tumbarello and Johnson

Table 3. Multivariate Logistic Regression Analysis of Risk Factors for Multidrug-Resistant Uropathogens and the Corresponding Weighted Points Values in Bacterial Community-Acquired Urinary Tract Infection Patients

Variables	Regression Coefficient	*P*	Adjusted OR 95% CI	Weighted Score
Age ≥70 y	0.95	<.001	2.6 (1.8–3.7)	4
Diabetes	0.49	.004	1.63 (1.17–2.3)	2
History of urinary tract surgery in the last 12 mo	1.4	.045	4 (1.1–14)	6
Previous antimicrobial therapy in the last 3 mo	1.6	<.001	5 (3.2–8)	6

Abbreviations: CI, confidence interval; MDR, multidrug-resistant; OR, odds ratio; UTI, urinary tract infection.

found that transfer from another health care facility, immunosuppression, and recent hospitalization were independent risk factors of MDR [9, 10]. Other risk factors of MDR have been reported, such as high dependency, assisted living, and nursing home residence [25, 26].

This study proposed a weighted score model based on simple information available on hospital admission. This enhances its practical value in clinical settings, and its consistent use might conceivably reduce the subsequent need for surveillance cultures. Other scoring systems have been performed in previous studies to predict specific resistant uropathogens. Both the Duke and the Italian models were suggested to predict infection with extended-spectrum β-lactamase-producing Enterobacteriaceae in UTI, including recent hospitalization, admission from another health care facility, Charlson comorbidity index ≥4, previous antimicrobial therapy, history of urinary catheterization, age ≥70 years, and immunosuppression [9, 10]. In another study, Faine et al. attempted to evaluate MDR in urinary tract infections in a specific ward (the emergency department) on the basis of a scoring system that included male gender, chronic hemodialysis, and nursing home residence [26]. Compared with other previous scoring systems, our predictive model had the advantages of being applicable to the general population consulting for a CUTI and not being restrictive to specifically high-risk patients. Another interesting point is that our model was not exclusively used for particular subgroups of uropathogens, such as β-lactamase producers, but included all the antibiotic resistance mechanisms of Enterobacteriaceae.

Our scoring system was relatively a good predictor of MDR in CUTI, and its performance depended on the cutoff value. At a threshold of ≥2, the sensitivity was relatively good, suggesting that only 29.3% of patients with MDR isolates would have failed to receive the necessary initial empiric directed at MDR. If only subjects with a score of 8 or above had been given empiric therapy adequately directed at MDR, 90% of patients would have received appropriate initial therapy and only 10% would have been treated too broadly. At a cutoff of 6, only 28.5% of patients with infections other than MDR bacteria would receive a broader treatment. This threshold was a suitable value for our population and would be a cost-effective strategy in Tunisia and other limited-resource countries. These findings were of great benefit for our country and could be generalized to those with a high MDR prevalence. As soon as microbiological data become available, antibiotic treatment should be de-escalated whenever appropriate to prevent the subsequent emergence of MDR bacteria. Using this score based on simple parameters available at first evaluation of the patient, we could predict patients with MDR CUTI and then reduce errors in prescribing empirical antibiotic therapy. It was notable that the chance of not covering a pathogen was dependent on the severity of illness.

Our study had some limitations. First, this was a retrospective study, which introduced the risk of incomplete information. Second, because of the highly varied incidence of MDR in different areas, it remains unclear where the predictor model is adequately applicable worldwide and if the cutoff value is suitable for a region with a high incidence. Although our model was internally validated using bootstrapping, our results should be independently validated. Consequently, multicenter and nation-wide studies are warranted to externally validate the clinical significance of this scoring system.

Table 4. The Sensitivity, Specificity, Predictive Values, and Diagnostic Accuracy of the Weighted Score Predictive of Multidrug Resistance With Various Cutoff Points in Bacterial Community-Acquired Urinary Tract Infections

Cutoff Point	Sensitivity, %	Specificity, %	PPV, %	NPV, %	DA, %
≥2	70.7	60	61	70	66
≥4	60	73.7	67	66	68
≥6	43	85	72.5	62	66
≥8	21	98	90	60	64
≥10	16	99	93.3	57	62
≥12	11	100	100	55	60

Abbreviations: DA, diagnostic accuracy; NPV, negative predictive value; PPV, positive predictive value.

CONCLUSIONS

Our study provided insight into the clinical predictors of MDR in CUTI. We developed a novel scoring system that can reliably identify patients likely to be harboring MDR uropathogens on hospital admission, based on 4 variables that are easy to define in clinical practice at the time of hospital admission. Proper use of this tool should minimize the time required to manage CUTI and could reduce workloads and costs. Future efforts should focus on quantifying its value as a risk assessment tool compared with the clinical decisions of physicians. Further validation works on this novel predictor should be perused to guide appropriate antimicrobial therapy and to improve the prognosis of these infections.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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